A

Synopsis on

Pharmacological Evaluation on Hepatoprotective and Antiulcer Potential of Selected Medicinal Plants of Uttarakhand Kumaun Region

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PROPOSED TITLE

Pharmacological Evaluation on Hepatoprotective and Antiulcer Potential of Selected Medicinal Plants of Uttarakhand Kumaun Region.

Rationale for Choosing Topic

The liver is the largest organ in the body carrying out most of the biochemical synthesis and secretary functions. Living in a world of inadequately controlled environment, pollution and expanding therapy with potent drugs liver is continuously exposed to variety of xenobiotics and therapeutic agents resulting in its structural or functional damage.

Likewise, Peptic Ulcer Disease (PUD) is a major disease of gastrointestinal tract, affecting almostone-tenth of the total world's population with different etiologies and its prevalence is also on the higher side in a country like India.

INTRODUCTION

HEPATOTOXICITY AND ITS IMPACT ON LIVER

One of the primary factors contributing to liver disease on a worldwide scale nowadays is the rising consumption of alcohol across all socio economic strata, in both developed and developing nations alike. Liver damage is prevalent due to drug usage. There are over one thousand drugs, toxins, and botanicals that have been discovered to cause damage to the liver. The pharmaceutical sector is responsible for twenty to forty percent of all cases of fulminant hepatic failure. More than seventy-five percent of people who have a negative reaction to a medication will either require a liver transplant or pass away as a result of their condition. Hepatitis brought on by drug use is the primary consideration when deciding whether or not to remove a medication from circulation. Because an early diagnosis can lead to a less severe case of hepatotoxicity if the drug in issue is discontinued, it is essential for medical professionals to be vigilant in their search for indications of drug-induced damage to the liver. Hepatotoxicity caused by drugs can manifest in a broad range of different ways, ranging from relatively minor elevations in liver enzyme levels to life-threatening hepatic failure. In order to make an accurate diagnosis of malnutrition, anaemia, infection, or the use of over-the-counter drugs that are toxic to the liver, one must be conversant with the typically relevant substances and have a high index of suspicion. The treatment of liver diseases with conventional medications, such as corticosteroids, anti-viral, and immunosuppressant drugs, is not always beneficial and can have significant adverse effects. Therefore, it is of the utmost importance to search for more effective drugs to treat diseases of the liver. In order to achieve this goal, the current study is focusing on locating the hepatoprotective and anti-ulcer drug that has the most potential and may be employed without risk in clinical settings.

While plants have historically been an essential resource for the discovery of new medicines, numerous plant species have been studied to identify whether or not they contain any chemicals that have the potential to be used in therapeutic applications. Plants used in traditional medicine have the potential to treat a variety of illnesses. Traditional remedies, the majority of which are derived from plants, may be found in abundance across the numerous cultural traditions that exist in our country. As a consequence of the recent surge in plant research that has been taking place all over the world, a sizeable body of evidence has accumulated to indicate the great potential of medicinal plants that are utilised in a variety of

traditional medical systems. More than 13,000 cases have been investigated by researchers during the previous five years. The development of new medicines derived from medicinal plants has received a significant boost as techniques for isolating chemical principles from natural sources have advanced and become more sophisticated. Traditionally, scientists who study infectious diseases have had a strong interest in biologically active compounds derived from natural sources. In recent years, there has been an increase in the number of scientific studies conducted on plants that are regarded as beneficial in the Ayurvedic medical system of India. It is imperative that further in-depth research be conducted into the chemistry and pharmacology of plant-based goods since it is possible that one day these fields will offer a treatment for many diseases.

ULCER :

Peptic ulcer is referred to by the Ayurvedic terms amlapitta, which literally translates to "pitta leading to sour taste," and parinamasula. These are the two phrases that are used the most frequently. The stomach is the organ most commonly impacted by the sickness known as amlapitta. According to Ayurvedic philosophy, there are five elements that make up everything: empty space, air, energy, liquid, and solid matter. The human body is composed of three different elements: vata (air and space), pitta (fire and water), and kapha (earth and goop) (liquid and solid). The terms vata, pitta, and kapha are referred to collectively as tridosha (three pillars of life). The characteristic feature of peptic ulcer disease (PUD) is the development of lesions in the mucosa (lining) of both the stomach and the first part of the small intestine (duodenum). These ulcers develop when the defensive forces that are present in the stomach, such as mucus, bicarbonate, and prostaglandins, are outnumbered by the aggressive factors that are present in the stomach, such as acid, pepsin, bile salts, and the helicobacter pylori bacteria. This condition is accompanied by a number of symptoms, some of which include a burning pain in the upper centre of the abdomen, a lack of appetite, a burning or aching pain in the epigastric region (Heart burn) that is worse at night, nausea, vomiting, bloating, belching, and a slow but steady loss of weight. Other symptoms include belching and a slow but steady loss of weight.

In addition to the food that we consume, the digestive tracts of our bodies are subjected to a wide range of other substances, some of which have the potential to cause harm to the lining of the stomach and intestines. Damage to the lining of the stomach and duodenum can be caused by a variety of factors, including prolonged use of oral medications (such as non-

steroidal anti-inflammatory drugs and steroids), bacterial infections (such as H. Pylori), chemicals produced by the body during digestion (such as gastric acid, pancreatic enzymes, and bile), and a lifestyle that is not healthy overall (Chronic alcoholism, Stress, Smoking). In order for our bodies to make use of the nutrients that are found in the food that we eat, the food must first be broken down through a process that is known as digestion. A highly developed immune system will typically try to both prevent infection and repair any harm that may have been done to the gastrointestinal (GI) mucosa. This defence mechanism also includes the production of mucus and various other chemicals (e.g., bicarbonate). Because of the operations of the immune system, compounds that help neutralise stomach (gastric) acid, and blood flow that renews and repairs the lining of the digestive tract, the digestive system is continually being replaced and repaired. This is possible thanks to the actions of the immune system. The development of ulcers (sores or lesions) in the stomach or duodenum can be the result of peptic ulcer disease, which can be brought on by inflammation, damage, or an underlying structural defect in the gastrointestinal tract.

Sores in the gastrointestinal tract that are greater than 5 millimetres and extend into the submucosal layer are referred to as peptic ulcers (sub-mucosa). Peptic ulcers that start in the lining of the stomach are referred to as gastric ulcers, whereas ulcers that begin in the duodenum are referred to as duodenal ulcers. A stomach ulcer is a moderate kind of intestinal erosion, and its medical name is "peptic ulcer." Peptic ulcers are sometimes referred to as "peptic ulcers." The condition that leads to stomach ulcers is very common and affects tens of millions of people all over the world. The size of an ulcer that develops in the stomach can range anywhere from a sixteenth of an inch to three quarters of an inch. Medications such as systemic antacids, Histamine (H2) receptor blockers, proton pump inhibitors, anticholinergics, prostaglandin analogues (PGE2), mucous protective drugs, and gram-negative antibiotics for H. pylori infection can be used to treat peptic ulcer disease. There is a possibility that using any of the medications listed above could result in adverse side effects such as convulsions, bradycardia, arrhythmias, coma, cardiac arrest, gynecomastia, loose stools, rashes, dizziness, joint pain, hepatic dysfunction, and so on.

Anti-cholinergic medications, histamine-H2 receptor antagonists, antacids, and, most recently, proton pumps inhibitors have revolutionised the treatment of peptic ulcers and other gastrointestinal illnesses. Despite these advancements, however, a long-term solution to this condition has not yet been discovered. It has been established a connection between the use of these medications for extended periods of time and a number of unfavourable outcomes

related to one's health. Relapses of the disease, ineffectiveness of various treatment regimens, and medication resistance are some of the emerging themes. In recent years, there has been a rise in the popularity of natural cures and supplementary treatments, particularly those that originate from plants. This trend is expected to continue. There is evidence to suggest that plant extracts may be a more promising drug discovery source for the treatment of stomach ulcers. So, it is of the utmost need to quickly identify an anti-ulcer drug that is more effective and safe.

REVIEW OF LITERATURE

Singh *et al.,* (2017) The efficacy of both the leaf and the bark of the member of the Moraceae family known as *Ficus racemosa* Linn to prevent ulcers in rats caused by ethanol and asprin was investigated. After being subjected to preliminary phytochemical screening for the presence of distinct phytocompounds in a variety of non-polar and polar solvents, crude medicinal extracts of *Ficus racemosa* leaves and bark were shown to have anti-ulcer activity. This was discovered after the extracts were given the opportunity to be tested. An experiment was carried out utilising the pylorus-ligation, ethanolic, and aspirin-induced ulcer models in order to assess the percentage of ulcer protection offered by the various polar and non-polar extracts of *Ficus racemosa*. In anti-ulcer models that included pylorus ligation, ethanol, and aspirin, methanolic extract of *Ficus racemosa* bark showed highly significant effectiveness ($p<.0001$) on % protection against ulcer formation. This extract was administered at doses of 200-400 mg/kg.

Abebaw *et al.,* (2017) The efficacy of an extract of the leaves of the plant belonging to the Santalaceae family, Osyris quadripartita Decne, to inhibit the development of ulcers in rats was investigated. The findings of this research indicate that OQ has a pharmacologic activity against ulcers without causing any acute toxicity when it is administered orally at the dosages that were investigated. It was shown to be as as beneficial, if not more so, when given numerous times rather than a single high dose when compared to the drugs that are considered the gold standard. It is possible that one or more of the phytochemicals discovered have actions that are anti-secretory and/or cytoprotective. Both of these actions may contribute to the anti-ulcer effects. As a result, the findings of this study provide credence to the use of OQ in the treatment of stomach ulcers in Ethiopian traditional medicine.

Martins *et al.,* (2014) Celtis iguanaea HE, a member of the Cannabaceae family, has been shown to be protective against the development of stomach ulcers in a number of different animal models. The gastroprotective activity of Celtis iguanaea HE has been linked to several different factors, including mucus, 2-adrenergic receptors, nitric oxide, and prostaglandins. From the leaves of Celtis iguanaea, phytoconstituents such as hydroxyl-linolenic acid, linoleic acids, and conjugated oxo-linoleic acids have been extracted (HE).

Pareek *et al., (*2013) It has been demonstrated that the ethanolic extract of the plant known as Fagonia schweinfurthii (Hadidi), which is a member of the Zygophyllaceae family, exerts a significant amount of hepatoprotective activity. It's possible that the extract's ability to

lower lipid peroxidation and increase anti-oxidant enzymatic activity is to blame for this result.

Deng *et al.*, (2012) findings suggested that the effect of EVT against CCl4 induced liver damage is related to its antioxidant properties, and that ethanol extract of Vitis thunbergia (EVT) belonging to family taiwaniana has antioxidant effects in vitro and hepatoprotective effect on acute liver injuries induced by CCl4 in vivo.

Shah *et al.*, (2011) An Ayurvedic preparation known as punarnavashtak kwath was tested for its ability to protect the liver from the damage caused by CCl4 in both rats and the HepG2 cell line. After consuming Punarnavashtak kwath (PNK), levels of many blood liver marker enzymes, including aspartate transaminase, serum alanine transaminase, serum alkaline phosphatase, and serum bilirubin, decreased, showing a significant hepatoprotective effect.

Gujrati *et al.*, (2007) The asclepiadaceae plant family, and more specifically the Tylophora indica (Linn) leaves, were investigated by scientists to see whether or not they may shield the liver from the damaging effects of ethanol. They found that the alcoholic extract of the leaves was just as effective as the water extract of the leaves. They came to the conclusion that extracts of both ALLT and AQLT possessed hepatoprotective qualities. There was a significant difference in the levels of hepatoprotective activity between the alcoholic extract and the aqueous extract. The alcoholic extract had the highest level.

Gaire *et al.*, (2011) Researchers examined the stem bark of the Ficus auriculata (Lour.) tree in order to investigate its potential antibacterial and antioxidant effects. After processing the stem bark with hexane, chloroform, and methanol in that order to obtain the extracts, four kilogrammes of dry bark pieces were macerated in a solvent consisting of methanol at room temperature for forty-eight hours. This process took place over the course of two days. In the methanol extract of Ficus auriculata lour. stem bark, a number of different phytochemicals, including alkaloids, flavonoids, sugars, saponins, glycosides, phytosterols, resins, phenols, tannins, di-terpenes, proteins, and amino acids, were found. Additionally, alkaloids and flavonoids were found to be present. At a concentration of 0.1 mg/ml, methanolic extract showed anti-oxidant activity of 84.088%, with an IC50 value of 0.042 mg/ml (r2 = 0.9942), whereas chloroform extract showed anti-oxidant activity of 83.864% at the same concentration. With a zone of inhibition of 4.5+-0.15 mm, the antibacterial activity of methanol extract was shown to be the most effective against Escherichia coli.

Madhulatha *et al.*, (2013) demonstrated that the Nyctaginaceae plant Pisonia aculeata Linn may inhibit the formation of stomach ulcers in rats that were given the pylorus-ligation paradigm to experience. At dose levels of 100 and 200 mg/kg body weight orally, many different Pisonia aculeata leaf extracts were investigated in a pylorus ligation induced stomach ulcer model in albino rats. Ranitidine, at a dosage of 30 mg/kg, was used as the gold standard for comparison. We found that a concentration of 200 mg/kg of Pisonia aculeata leaf extract had significant anti-ulcer efficacy when compared to the gold standard. This finding was made after various different Pisonia aculeata leaf extracts were examined.

AIM AND OBJECTIVES

Aim- The study is designed to evaluate the Hepatoprotective and Antiulcer potential of selected medicinal plants of Uttarakhand kumaun region.

Objectives:

- To study the anti-ulcer potential by various models of gastric ulcers and to evaluate effect on gastric secretion and gastric cytoprotection.

Pylorus-ligation induced gastric ulcer.

Ethanol induced gastric ulcer.

NSAID'S induced gastric ulcer.

- Study of biochemical parameters for ulcer.

Determination of free acidity.

pH.

Ulcer index.

Gastric Volume.

No. of ulcers (Ulcer score).

- To Investigate the hepatoprotective potential in following models.
- Paracetamol induced hepatic injury in Rats.
- Ethanol induced Liver Toxicity Model in Experimental Animals.
- Determination of several biochemical parameters.
  - Bilirubin,
  - AST
  - ALT,
  - Total protein
  - SGPT
  - SGOT

Research Envisaged

Traditional remedies are held in extremely high regard and importance when it comes to the treatment of medical conditions. The vast majority of people in third world countries continue to cure common illnesses with traditional remedies made from locally found ingredients.

Hepatotoxicity as well as ulcer affects younger and elder patients equally. It occurs as a unwanted gift in the present life style of the individuals. The available drugs in the market have untoward side effects. Traditionally different plants and their parts are used to treat hepatic and ulcer related problems from many centuries. However no scientific data backing is available to support thesame. Therefore present research work is an attempt to evaluate hepatoprotective and anti-ulcer activity of some unexplored medicinal plants and their combined form. This work is based on the traditional approach to pass the advantages of herbs to mankind with proper and effective scientific data . For the same positive approach we will take two or three plants for pharmacological screening from these plants as these are yet not been explored for above activity. Selection of these plants is based on their nature and type of chemical constituents or traditional application. Above work is an attempt to provide some newer therapeutic option to physicians in hepatotoxicity and ulcer management.

PLAN OF WORK

The entire work has been divided into following steps:

- Exhaustive literature survey.
- Authentication of Plants.
- Collection of different desirable parts of plant.
- Plant Extraction.
- Phytochemical Screening.
- Toxicological study as per OECD guidelines.
- Pharmacological screening of individual plant extracts.
    - Animal selection- Male wistar rats weighing 150-200 gm.
    - Models used for assessment of anti-ulcer activity.
        - Shay pylorus ligation in rats.
        - Ethanol induced ulcer

Animals required for Anti-ulcer activity

(Male wistar rats -36)

Animals required for Hepatoprotective activity

(Male wistar rats-36)

- Study of Biochemical Parameters.
- Pharmacological screening of individual plant extracts for Hepatoprotective Potential.
- Models used for assessment of Hepatoprotective activity.
    - Paracetamol induced hepatic injury in rats.
    - Ethanol induced liver toxicity in experimental animals.
- Histopathological examination.
- Statistical analysis.
- Compilation of findings and Thesis writing

RESEARCH METHODOLOGY.

1. Authentication and collection of plant.
2. Preparation of plant extract and their qualitative analysis.
3. Animal selection and Screening of different plant extracts for Hepatoprotective and Anti-ulcer activity on different animal models.

4. Study of Biochemical Parameters.
5. Pathological examination for microscopic evaluation.
6. All the outcomes obtained will be analysed by using suitable statistical methods and using software programmes like SPSS and graph pad prism.

STATISTICAL TOOLS:

The data will be presented as the mean accompanied by the standard error, and comparisons between means will be made using a one-way analysis of variance and Scheffé's test for multiple comparisons.

Models for Anti - Ulcer Activity : -

- **Shay pylorus ligation in rats-** There will be a total of 36 animals utilised for this experiment, and they will be divided up into six groups of six to serve as the standard, positive control, negative control, test 1, test 2, and test 3 doses, respectively. In order to get them ready for the experiment, male Wistar rats will have to abstain from food for a full day while they are allowed to drink water. The only thing that will be done for the animals that have been allotted to the control group is to transport them. The standardisation of the plan extract will allow for greater dosage flexibility. We will employ the gold standard dose of rabeprazole, which is 20mg/kg of the drug delivered intraperitoneally, while control rats will get vehicle. After administering the medication for one hour, animals will be put to sleep with the help of thiopental sodium, which will be given to the animals. In order to gain access to the abdominal cavity, a very small incision will be made in the midline, right below the xiphoid process. The Shay technique entails carefully replacing the stomach without putting any tension on the pylorus or cutting off its blood supply. This allows the pyloric portion of the stomach to be ligated in a way that prevents stomach acid from damaging the pylorus. At this point, the stomach is relocated with great care, and interrupted sutures are used to close the abdominal wall. At the end of the fourth hour following pyloric ligation, rats are put to death by receiving an overdose of sodium thiopental through an injection.

ULCER INDEX :-

$$\mathbf{U.I = UN + US + UP \times 10^{-1}}$$

U.I :- Ulcer Index.

UN :- Average of no. of ulcer's.

US :- Average of severity score.

UP :- % of animal with ulcer.

- **Ethanol induced ulcer-** Animals are allowed access to water throughout the fasting period of twenty-four hours that precedes an experiment. A random selection is made from each of the three categories of animals: control, standard, and test. To each and every one of the rats, an oral dose of 200gm/ml of ethanol that is 90% strength is given. Oral administration of the extracts that were tested during the study. When it comes to rabeprazole, the normal dose is 20 milligrammes per kilogramme, whereas the group receiving the placebo just gets vehicle (p.o.). When an hour has passed, the animals who were given the treatment are put to sleep with a dose of ether that is sufficient to cause death, their stomachs are surgically removed, and their stomachs are cut with increased curvature to determine the ulcer index.

- **Paracetamol induced Hepatotoxicity in Rats:-**

Animals (male wistar rats) will be allocated in different groups and pretreated with control,test and standard (Paracetamol at chronic doses), separately and with standard for 21 days. Blood samples will be taken after 7 and 21 days for estimation. After 21 days animals will be sacrificed by deep anesthesia and abdomen and liver will be used for further study.

- Study of Biochemical Parameters.
- Bilirubin,
- AST
- Total protein
- SGPT, SGOT
- Histopathological examination.

- **Statistical analysis.**
- **Compilation of results**
- **Thesis writing and publication of study**

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